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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003906771 for a patent by BIOSIGNAL PTY LTD as filed on 05 December 2003.

WITNESS my hand this
Twenty-second day of December 2004

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES



AUSTRALIA

Patents Act 1990

Biosignal Pty Ltd

PROVISIONAL SPECIFICATION

Invention Title:

Antimicrobial polymers

The invention is described in the following statement:

FIELD OF THE INVENTION

This invention relates to antimicrobial polymers. In particular, this invention relates to silicone polymers (e.g. silanes, siloxanes, silicone rubbers etc) associated with antimicrobial compounds.

BACKGROUND OF THE INVENTION

Fimbrolides (halogenated 5-methylene-2(5H)-furanones) possess a wide range of important biological properties including antifungal and antimicrobial properties. These metabolites can be isolated from red marine algae *Delisea fimbriata*, *Delisea elegans* and *Delisea pulchra*, and a variety of structurally related furanones (e.g. degree and position of substitution of halogen on the furanone ring system, type of heteroatoms present in the furanone ring, and the length and position of the sidechain with respect to the furanone carbonyl group) can be derived through synthesis. Halogenated furanones regulate the phenotypes of Gram positive and Gram negative bacteria, and interfere with their settlement and motility on treated surfaces (see for example PCT/AU95/00407, PCT/AU96/00167, PCT/AU99/00285, PCT/AU99/00284, PCT/AU00/01553, PCT/AU01/00296, PCT/AU01/00295, PCT/AU01/00407, PCT/AU01/00781 and PCT/AU01/01621, the disclosures of which are incorporated herein in their entirety by cross-reference.

Bacterial biofilms are undesirable on many types of surfaces. Such surfaces include, for example, cooling water towers, household and industrial cleaning surfaces, biomedical devices and electronic devices. Currently chemical biocides such as bleach, ammonia, quaternary ammonium salts and strong alkaline solutions are used to remove such biofilms. These chemical biocides may have a harmful effect on the environment. Therefore, the use of naturally derived antimicrobial compounds or derivatives thereof are becoming increasingly desirable and necessary.

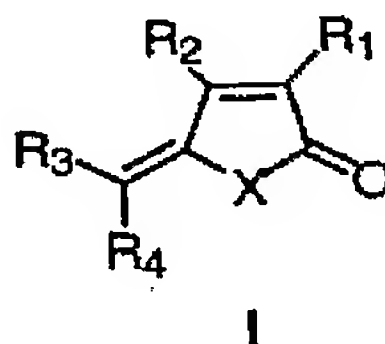
The present inventors have found that furanone compounds and the like can be incorporated into silicon polymers and these polymers can be used in protecting a wide range of devices and equipment from biological damage due to Gram-negative and Gram-positive and fungi.

The antimicrobial oligomer or polymer may be an elastomer or rubber. The elastomer or rubber may be extensively cross-linked. The antibacterial oligomer or polymer of the present invention may be, or form part of, a curable or vulcanisable composition. Silicone elastomers may be high molecular weight linear polymers. These can be cured by a number of ways, for example, by free radical cross linking (eg using benzoyl peroxide) to form bridges between the chains; by crosslinking vinyl groups attached to silicon through reaction with silylhydride groups; by crosslinking linear or branched siloxane chains having reactive end groups such as silanols to yield Si-O-Si crosslinks. These materials have outstanding low temperature flexibility, are stable at high temperatures and are resistant to weathering and lubricating oils. They may be used in gaskets and seals, wire and cable insulation, and hot gas and liquid conduits. They also have application in surgical and prosthetic devices. Curable room temperature vulcanising silicone elastomers have application in caulking, sealing and encapsulating.

The polymer or oligomer may form the whole, or part, of a shaped article. For example, the oligomer or polymer may be cured, cast or extruded to form a desired shape or a device. The antibacterial oligomer or polymer of the present invention may be, or comprise at least part of, a film or sheet.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the present invention, the antimicrobial silicone oligomer or polymer comprises a compound of formula I blended or mixed therewith,



wherein, R₁ and R₂ are independently H, halogen, alkyl, alkoxy, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophilic or fluorophilic;

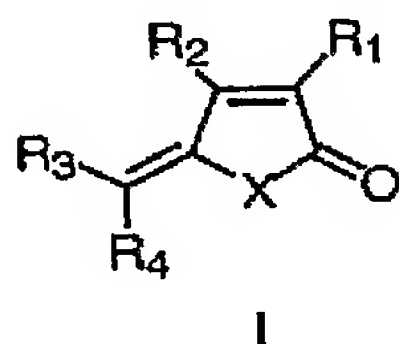
R₃ and R₄ are independently H, halogen, alkyl, aryl or arylalkyl; and

X is O or NR₂.

Preferably at least one of R₁, R₂, R₃ and R₄ is halogen, most preferably bromine.

The silicon oligomer or polymer can be a linear or cross-linked polymer, or a cyclic polymer. Non-limiting examples of silicon oligomer or polymer include hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, tetradecamethylhexasiloxane, hexamethyltricyclosiloxane, decamethylpentacyclosiloxane, dodecamethylhexacyclosiloxane, dimethylpolysiloxane. It is known in the art that the silicon rubber can be fabricated by a molding process (including liquid injection molding, transfer and compression molding) or an extrusion process by mixing and curing silicone with a catalyst and filler. In this invention the furanone can be optionally mixed with silicon or a cross linker or catalyst during the production of silicon oligomer or polymer. The polymer may be a homopolymer or copolymer.

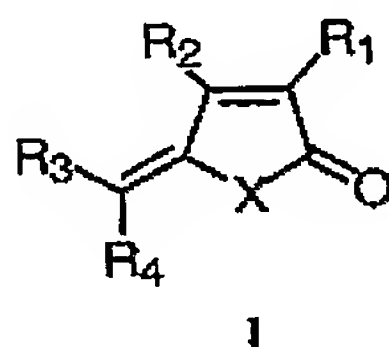
In a further embodiment, the present invention provides an oligomer or polymer according to the first aspect of invention, wherein the compound of formula I is adsorbed to the polymer or oligomer,



wherein X, R₁, R₂, R₃ and R₄ are as described above.

The compound of formula I may be adsorbed to the silicone polymer by direct application to the compound of formula I to the polymer. For example a material or device having at part of its surfaced formed from the polymer may be treated by either dip coating or painting the surface of the device with a solution of compound. The device or material may be a molded, extruded or assembled device. Examples of devices or materials include catheters, drain and fluid tubes, sheathing, shunts, pulmonary devices, laparoscopic devices, occluders, ear plugs, hearing aids, seals/stoppers/valves, septums etc.

In a further aspect the present invention provides an antimicrobial silicone oligomer or polymer formed by copolymerising a compound of formula I



with at least one silicone comonomer or oligomer and optionally at least one other monomer,

wherein R₁ and R₂ are independently H, halogen, alkyl, alkoxy, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophilic or fluorophilic;

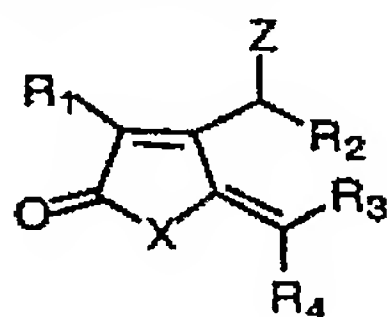
R₃ and R₄ are independently H, halogen, alkyl, aryl or arylalkyl; and

X is O or NR₂.

Preferably, at least one of R₁, R₂, R₃ and R₄ is halogen.

Non-limiting examples of silicon oligomer or polymer include hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, tetradecamethylhexasiloxane, hexamethyltricyclosiloxane, decamethylpentacyclosiloxane, dodecamethylhexacyclosiloxane, dimethylpolysiloxane.

Preferably the compound of the formula I is a compound of formula II



wherein R₁, R₂ are independently selected from H, alkyl, alkoxy, polyethyleneglycyl, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophobic, hydrophilic or fluorophilic;

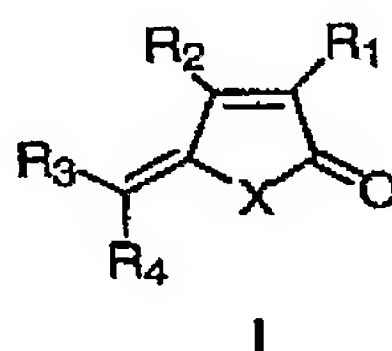
R₄ is a hydrogen, halogen (X = F, Cl, Br or I);

R₃ is hydrogen or halogen; and

X is O or NR₂ and

Z is independently selected from the group R_2 , halogen, OH, OOH, $OC(O)R_2$, $=O$, amine, azide, thiol, mercaptoalkyl, mercaptoalkenyl, alkenyloxy, aryloxy, mercaptoaryl, arylalkoxy, mercaptoarylalkyl, $SC(O)R_2$, $OS(O)_2R_2$, $NHC(O)R_2$, $=NR_2$, NHR_2 or silyloxy.

In a yet a further embodiment, the present invention provides an antimicrobial silicone oligomer or polymer formed by condensation polymerisation of a silicone monomer or oligomer or polymer with a compound of formula I



wherein R_1 and R_2 are independently H, halogen, alkyl, alkoxy, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophilic or fluorophilic;

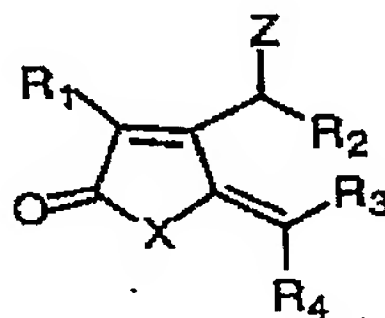
R_3 and R_4 are independently H, halogen, alkyl, aryl or arylalkyl;

X is O or NR_2 .

Preferably, at least one of R_1 , R_2 , R_3 and R_4 is halogen.

The silicon oligomer or polymer can be a linear or cross-linked polymer, or a cyclic polymer. Examples of silicon oligomer or polymer include hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, dodecamethylpentasiloxane, tetradecamethylhexasiloxane, hexamethyltricyclosiloxane, decamethylpentacyclosiloxane, dodecamethylhexacyclosiloxane, dimethylpolysiloxane.

Preferably the compound of the formula I is a compound of formula II;



II

wherein R_1, R_2 is a H, alkyl, alkoxy, polyethyleneglycyl, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophobic, hydrophilic or fluorophilic;

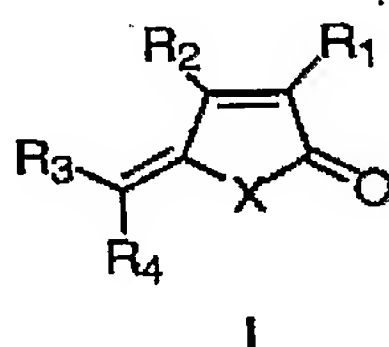
R_4 is a hydrogen, halogen ($X = F, Cl, Br$ or I);

R_3 are independently or both hydrogen or halogen;

X is O or NR_2 and

Z is independently selected from the group R_2 , halogen, OH, OOH, $OC(O)R_2$, $=O$, amine, azide, thiol, mercaptoalkyl, mercaptoalkenyl, alkenyloxy, aryloxy, mercaptoaryl, arylalkoxy, mercaptoarylalkyl, $SC(O)R_2$, $OS(O)_2R_2$, $NHC(O)R_2$, $=NR_2$, NHR_2 or silyloxy.

In yet a further embodiment, the present invention provides an antimicrobial silicone polymer formed by surface attachment of a compound of formula I on to a silicone polymer or a device formed at least in part therefrom



wherein R_1 and R_2 are independently H, halogen, alkyl, alkoxy, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophilic or fluorophilic;

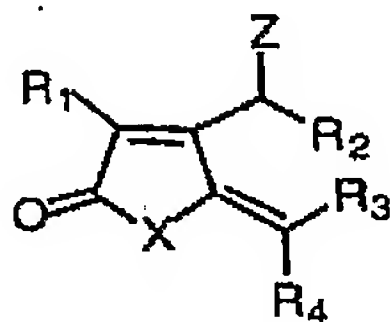
R_3 and R_4 are independently H, halogen, alkyl, aryl or arylalkyl; and

X is O or NR_2 .

Preferably at least one of R_1, R_2, R_3 and R_4 is halogen.

It is known in the art surface attachment of a compound to a polymer surface may require the initial activation of a surface by chemical means or plasma activation. The silicon polymers or devices used in this invention may be optionally chemically or plasma treated.

Preferably the compound of the formula I is of formula II,



II

wherein R_1 , R_2 is a H, alkyl, alkoxy, polyethyleneglycyl, oxoalkyl, alkenyl, aryl or arylalkyl whether unsubstituted or substituted, straight chain or branched chain, hydrophobic, hydrophilic or fluorophilic;

R_4 is a hydrogen, halogen ($X = F, Cl, Br$ or I);

R_3 are independently or both hydrogen or halogen;

X is O and NR_2 and

Z is independently selected from the group R_2 , halogen, OH , OOH , $OC(O)R_2$, $=O$, amine, azide, thiol, mercaptoalkyl, mercaptoalkenyl, alkenyloxy, aryloxy, mercaptoaryl, arylalkoxy, mercaptoarylalkyl, $SC(O)R_2$, $OS(O)_2R_2$, $NHC(O)R_2$, $=NR_2$, NHR_2 or silyloxy.

In yet a further aspect, the present invention includes a shaped article or a device formed at least in part from an antimicrobial polymer or oligomer of the present invention. The shaped article or device may be formed by curing, casting or extruding the polymer to a desired shape or a device.

As will be recognised by those skilled in the art, compounds of formulae I and II can exist in two isomer forms. It is not intended that the compounds of formulae I and II be limited to any particular isomer and so the present invention extends to all isomers of the compounds defined by the formulae.

The present invention also extends to methods of making the antimicrobial polymers and oligomers of the invention.

In a further aspect, the present invention provides a compound of formula III that is of formula I and having at least one $-YC(O)NR_7R_5Si(OR_6)_3$ group, where Y is selected from the group $O, S, N, P, C(O)$; R_5 is a linker and preferably is substituted or

unsubstituted alkyl, alkylaryl, arylalkyl, aryl, alkenyl, or a linker comprising these groups, optionally interrupted by one of more heteroatoms (eg oxygen), or a linking group comprising these groups and each R_6 is independently selected from substituted or unsubstituted alkyl, cycloalkyl, alkenyl or the like and R_7 is H or alkyl.

In a further aspect, the present invention provides a method of producing a compound according to formula III, comprising reacting a compound of formula I having at least one group selected from $-Y'-H$, wherein $-Y'$ is selected from the group O, S, NH, COO with a compound of formula $OCNR_5Si(OR_6)_3$, wherein R_5 and R_6 are as defined above.

In yet a further aspect, the present invention provides a method for associating a compound of formula III with surface, the method comprising contacting the compound of formula III with the surface and optionally curing the compound.

The surface may be treated to produce groups that are reactive with the silyloxy group of the compound of formula III.

The compound of formula III may also be associated with an oligomer or polymer as described. The oligomer or polymer may be an antimicrobial silicone oligomer or polymer as described above. Alternatively the compound of formula III, may be associated with a non-silicone oligomer or polymer, surface or device. The present invention also extends to an oligomer or polymer associated with a compound of formula III.

The antimicrobial polymers of the present invention have application in those applications in which silicone polymers or oligomers are used. Silicone polymers are incorporated into medicines; used in food processing (for example, canning and ready meals); used in a wide range of medical devices; used as putty and sealants. Silicone is also used in domestic and personal products such as cleaning solvents, handcream, hair and skin products, and antiperspirants.

The antimicrobial silicone polymers and oligomers of the present invention may be suitable for the following non-limiting applications -silicone impregnated electrical insulating tapes, silicone rubber, adhesives, sealants, elastoplastic resins for coatings of circuit boards, compounds for potting and protecting semiconductor devices, dielectric

compounds, high-purity coatings, varnishes, resins, specialty lubricants, optical fibre coatings and fibre optic cable filler, and semiconductor-grade silicon and silicon-source chemicals, windshield and canopy gasket sealants, rubber tooling for radome fabrication, optical interlayer laminates, abrasion-resistant coatings, adhesives, seals and gaskets, and tooling materials, construction adhesive/sealants, glazing adhesive/sealants and elastomers, silicone/polyurethane foam roof coatings, fire retardant foams and sealants, architectural coatings and water repellents, concrete pavement joint sealants, antifoams, bakeware coatings; processing aids for food processing applications; automotive applications including heat, oil and fuel-resistant silicone rubbers; one or two part sealants and adhesives, specialty lubricants and materials for noise, vibration, harshness and thermal management, automotive polishes; adhesives including silicone elastomers, adhesives, sealants, dielectric compounds, varnishes, multi-purpose silicone fluids, antifoams, release agents, surfactants, maintenance lubricants, elastomers and greases; medical applications and medical products including medical-grade tubing, adhesives, defoamers and fluids; textiles and leather applications, for example, waterproofing treatments and fibre chemicals; silicone adhesives, sealants and caulks for home improvement and renovation by do-it-yourselfers; paints and coatings applications, for example silicone additives for high-performance paints, enamels, finishes and abrasion resistant coatings for plastics; silicone rubber compounds for temperature and chemical resistant printing equipment component; applications in plastics, for example, mold release additives, catalyst modifiers, and chemicals for high-performance plastics applications; pressure sensitive adhesives, for example, release coatings for backings on tapes, labels, stamps, stickers, decals and food packaging; pressure-sensitive adhesives; personal and household care, for example, surfactants, emulsions, fluids and powder treatments are important ingredients in skin and suntan lotions, anti-perspirants and deodorants, hair care products, shaving creams, cosmetics, starches, fabric treatments, laundry products hair care products; pharmaceutical applications, for example, medical-grade fluids, emulsions, antifoams, adhesives and silicone rubber tubing; medical devices, for example, heart valves, contact lenses, surgical equipment, catheters, drain and fluid tubes, sheathing, shunts, pulmonary devices, laparoscopic devices, occluders, ear plugs, hearing aids, seals/stoppers/valves, septums etc temporomandibular joint (jaw) implants; small joint orthopaedic (finger) implants; large joint products (hip, knee, elbow) implants; long term implantable contraceptives; silicone fluids for injection and certain custom silicone implant products; cleaning applications including toilet cleaners and industrial cleaning agents, membranes, water filters, air conditioning and cooling towers.

Definitions

The term "alkyl" is taken to include both straight chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, and the like. Preferably the alkyl group is a lower alkyl of 1 to 6 carbon atoms. The alkyl group may optionally be substituted by one or more groups selected from alkyl, cycloalkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkynyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, amino, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroheterocyclyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulfenyl, alkylcarbonyloxy, alkylthio, acylthio, silyloxyalkyl, phosphorus-containing groups such as phosphono and phosphinyl.

The term "alkoxy" includes straight chain or branched alkyloxy, preferably C1-10 alkoxy. Examples include methoxy, ethoxy, n-propoxy, isopropoxy and the different butoxy isomers.

The term "alkenyl" includes groups formed from straight chain, branched or mono- or polycyclic alkenes and polyene. Substituents include mono- or polyunsaturated alkyl or cycloalkyl groups as previously defined, preferably C2-10 alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl, or 1,3,5,7-cyclooctatetraenyl.

The term "halogen" denotes fluorine, chlorine, bromine or iodine, preferably bromine or fluorine.

The term "heteroatoms" denotes O, N or S.

The term "acyl" used either alone or in compound words such as "acyloxy", "acylthio", "acylamino" or diacylamino" includes an aliphatic acyl group and an acyl

group containing a heterocyclic ring which is referred to as heterocyclic acyl, preferably a C₁-10 alkanoyl. Examples of acyl include carbamoyl; straight chain or branched alkanoyl, such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl or heptyloxycarbonyl; cycloalkanecarbonyl such as cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl or cyclohexanecarbonyl; alkanesulfonyl, such as methanesulfonyl or ethanesulfonyl; alkoxysulfonyl, such as methoxysulfonyl or ethoxysulfonyl; heterocycloalkanecarbonyl; heterocyclyoalkanoyl, such as pyrrolidinylacetyl, pyrrolidinylpropanoyl, pyrrolidinylbutanoyl, pyrrolidinylpentanoyl, pyrrolidinylhexanoyl or thiazolidinylacetyl; heterocyclylalkenoyl, such as heterocyclylpropenoyl, heterocyclylbutenoyl, heterocyclylpentenoyl or heterocyclylhexenoyl; or heterocyclylglyoxyloyl, such as, thiazolidinylglyoxyloyl or pyrrolidinylglyoxyloyl.

The term "substituted" includes substitution by one or more groups selected from alkyl, cycloalkyl, alkenyl, alkynyl, halo, haloalkyl, haloalkynyl, hydroxy, alkoxy, alkenyloxy, haloalkoxy, haloalkenyloxy, nitro, amino, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroheterocyclyl, alkylamino, dialkylamino, alkenylamine, alkynylamino, acyl, alkenoyl, alkynoyl, acylamino, diacylamino, acyloxy, alkylsulfonyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulfenyl, alkylcarbonyloxy, alkylthio, acylthio, phosphorus-containing groups such as phosphono and phosphinyl.; $-YC(O)NR_5Si(OR_6)_3$, where Y is selected from the group O, S, N, P, C(O), R₅ is a linker group which may be, for example, substituted or unsubstituted alkyl, alkylaryl, arylalkyl, aryl, alkenyl, optionally interrupted by one or more heteroatoms and each R₆ is independently selected from substituted or unsubstituted alkyl, cycloalkyl, alkenyl or the like.

The term "fluorophilic" is used to indicate the highly attractive interactions between certain groups, such as highly fluorinated alkyl groups of C₄-C₁₀ chain length, have for perfluoroalkanes and perfluoroalkane polymers.

The one or more other monomer may be any suitable polymerisable copolymer e.g. acrylate ester such as alkyl, hydroxyalkyl, aminoalkyl, or substituted aryl acrylates or methacrylates, crotonates, substituted or unsubstituted acrylonitriles, vinyl alcohols or acetates, styrene and siloxanes.

The present invention will now be described with reference to the following non-limiting examples of the invention.

EMBODIMENTS

Example 1

A siloxane polymer with adsorbed furanone is prepared by soaking a silicone polymer or a device in a solution of 3-(1'-bromooctoyl)-4-bromo-5-bromomethylene-2(5H)-furanone, in an organic solvent.

Example 2

A condensation siloxane polymer is synthesised by heating a mixture of polydimethylsiloxane (PDMS) and 3-(1'-hydroxydodecyl)-5-dibromomethylene-2(5H)-furanone.

Example 3

A copolymerised siloxane polymer is synthesised by heating a mixture of methyl methacrylate (MMA), 3-(1'-acryloyloxydodecyl)-5-dibromomethylene-2(5H)-furanone, polydimethylsiloxane (PDMS) and (AIBN) in toluene at 70°C.

Example 4

A crosslinked siloxane polymer is synthesised by heating a mixture of 3-(1'-acryloyloxybutyl)-4-bromo-5-bromomethylene-2(5H)-furanone and polydimethylsiloxane (PDMS) in the presence of a platinum catalyst.

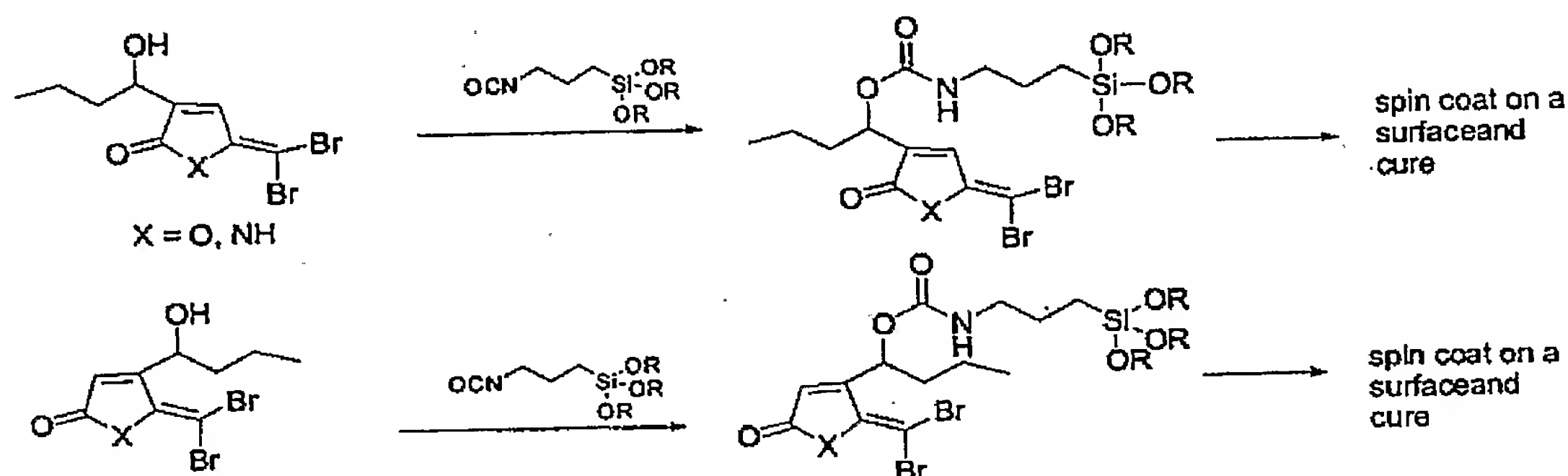
Example 5

A copolymerised siloxane polymer is synthesised by heating a mixture of styrene, 3-(1'-bromohexyl)-4-bromo-5-bromomethylene-2(5H)-furanone, polydimethylsiloxane (PDMS) and (AIBN) in toluene at 70°C.

Example 5 General procedure for production of compound III

A mixture of equivalent amount of furanone alcohol and silyloxypropyl isocyanate in dry dichloromethane was stirred at room temperature for 3h. The resulting solution was concentrated and spin-coated on a glass or metal surface. The resulting film was cured

either by heating at 120 degrees celcius or at room temperature for 24h. The presence of furanone on the surface of the film was established by XPS analysis.



The alcohol group could be present any where in the molecule e.g.



Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Finally, it will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The

present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this fourth day of December 2003

Biosignal Pty Ltd
Patent Attorneys for the Applicant:

F B RICE & CO